UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,324	10/07/2005	Hans Loibner	4518-0111PUS1	8937

2292 7590 01/10/2008

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
01/10/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,324	LOIBNER ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *4, 6-8, 10 and 14-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,9,11-13,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/7/05; 5/22/06; 8/22/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. ____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-30 are all the pending claims for this application.

2. New claims 29 and 30 were added in the Reply of 10/25/07.

Election/Restrictions

3. Applicant's election of Group I (Claims 1-13 and new Claims 29 and 30) in the reply filed on 10/25/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 14-28 are withdrawn withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/25/07.

5. Applicant's election of species for a carbohydrate antigen (Lewis-Y, Sialyl-Tn and Globo H) in the reply filed on 10/25/07 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

6. Non-elected species for peptide/protein antigens and glycolipid antigens in Claim 9 are withdrawn from examination. Additionally, because Claim 4 reads on a peptide/protein antigen for Ep-CAM mimotope and is considered as being drawn to a non-elected species of antigen, Claim 4 and dependent Claims 6-8 and 10 are withdrawn from examination.

7. Claims 1-3, 5, 9, 11-13, 29 and 30 are all the pending claims under examination.

Information Disclosure Statement

8. The IDS of 10/7/05 did not provide copies of any cited references but the same references are cited and copies thereof provided in the IDS of 8/22/07. Therefore, the Examiner has stricken the references on the 1449 form of 10/7/05 IDS attached hereto. The references cited in the IDS of 5/22/06 have also been considered. An initialed copy of the 1449 form is attached hereto. The IDS of 8/22/07 recites the same two WO references cited in the IDS of 5/22/06, thus to avoid redundancy under 37 CFR 1.97 the references in the 1449 form of 8/22/07 have been stricken. Furthermore, ref #AB (Haroon US20040181475) in the IDS of 8/22/07 does not appear to be relevant or related to the instant application and this reference has been stricken on the attached 1449 form. Otherwise, the references in the IDS 8/22/07 have been considered and entered.

Specification

The disclosure is objected to because of the following informalities:

9. The text on pp. 9, 23, 24 appears to omit a symbol with reference to, for example, "□-Gal epitopes (Gal □ 1,3,Galβ1,4GlcNAc-R)", ""□-gal eptope" and "□1,3,Galactosyltransferse" (p. 9); "Maxisorp□" and "Novex□" (p. 23); and "□ 215 and □ 218 nm" (p. 24). Correction is required.

Applicants are requested to carefully check the entire specification for any other similar omissions.

Applicants are also requested to identify original proof for any amendments to avoid introducing new matter.

10. The use of trademarks, e.g., "Protein A Sepharose®", has been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicants are advised to carefully check the entire specification for any other improperly identified trademarks.

11. The guidelines under 37 CFR 1.77(b) illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

a) The specification is objected to for failing to provide a cross-reference to the priority documents for this application.

b) The Brief Description of the Drawings on pp. 19-20 should be inserted between the Summary of the Invention and the Detailed Description of the Invention.

c) The Abstract of Disclosure is a virtual copy of the abstract from the corresponding WO reference and should appear as a separate sheet to the specification.

12. The figure legends for Figures 1-10 are objected to because they do not describe in brief but sufficient detail the data depicted in any of the figures. Furthermore, Figures 2, 3 and 6-9 are objected to because the figures recite nucleic acid or protein sequences which are required under 37 CFR 1.821(c) to be identified by SEQ ID NO. Correcting the figure legends for Figures 2, 3 and 6-9 to insert the SEQ ID NOS would overcome the objection.

Claim Objections

13. Claims 5, 9 and 30 are objected to because of the following informalities:

a) Claims 5, 9 and 30 are inconsistent in the spelling for the carbohydrate: "Lewis-y" (Claim 5) and "Lewis Y" (Claims 9 and 30).

b) Claim 12 recites "CHI" which is an apparent misspelling for "CH1".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-3, 5, 9, 11-13, 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-3, 5, 9, 11-13, 29 and 30 are indefinite for the recitation "comprising at least a part of a murine IgG2a subtype amino acid sequence" in Claim 1 because it is not clear what portion of a murine IgG2a antibody is encompassed by the scope of the claims. The claims encompass both variable and non-variable domains including the hinge and constant domains, and portions thereof. For example, are applicants contemplating single CDR domains much less fragments of a CDR domain from any IgG2a antibody?

b) Claims 2, 3, 5, 29 and 30 are indefinite for the recitation ""or fragments thereof" in Claims 2 and 3 because it is not clear if the limitation is referring to the

antibody, the epitope or the tumor associated antigen of Claim 2; or the antibody, the mimitope or the tumor associated antigen of Claim 3.

c) Claims 9, 11 and 12 recite the limitation "the antigen" in Claim 9. There is insufficient antecedent basis for this limitation in the claim or in Claim 1 from which the claims depend.

d) Regarding claim 9, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

e) In view of the Claim 9 reading on carbohydrates as the antigen for the Markush group, the claim recites improper Markush group language for the species "Lewis Y, Sialyl-Tn, Globo H". See MPEP 803.02 for Markush group language.

f) Claim 12 recites improper Markush group language; the recitation "selected from the" is incomplete. See MPEP 803.02 for Markush group language.

g) Claim 12 is indefinite for the recitation "the IgG2a subtype amino acid sequence is contained in at least one of the regions selected from the CHI [*CH1*], hinge, CH2 and CH3 regions" because it is not clear how just any portion from the IgG2a sequence can be inserted into (or between) more than any one of the constant domain regions of the IgG1 antibody without affecting the binding of the acceptor antibody. The claim now reads on multiple insertions occurring within the hinge, CH1, CH2 and/or CH3 of the IgG1 antibody by any part of the murine IgG2a amino acid sequence. This could include variable domains or even CDRs from the murine IgG2a antibody being inserted into various regions of the constant domain of the IgG1 antibody.

h) Claim 13 is indefinite for the recitation "monoclonal antibodies produced by ATCC HB 9324 or ATCC HB 9347" because it is unclear how an antibody can be produced from an ATCC accession no. The art teaches that a hybridoma is produced by the fusion between a B cell and a myeloma cell, which is a cancer cell that provides the resultant B cell-myeloma hybrid, or hybridoma, with the capacity to proliferate indefinitely and to secrete the full length monoclonal antibody having a single idiotype (see Campbell et al, Biology, 5th ed. pg. 856, 1999). Thus, when read in light of the specification and in view of the knowledge in the art, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of "monoclonal antibodies produced by ATCC HB 9324 or ATCC HB 9347" as presently claimed because a hybridoma secretes or produces full length mouse antibodies. It is unclear what is contemplated by the phrase and one of skill in the art could not determine the metes and bounds of the claimed invention as written.

i) Claim 30 is indefinite for the recitation "said carbohydrate is *a number* selected from the group consisting of." The claim either recites improper Markush group language (see MPEP 803.02) or the intended species of the Markush group should be a number rather than the species of carbohydrates as set forth.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit Requirement

15. Claim 13 is rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description.

a. It is unclear if a hybridoma cell line which produces an antibody having the exact chemical identity of the antibody produced by the hybridoma designated ATCC HB 9324 or ATCC HB 9347 is known and publicly available, or can be reproducibly isolated without undue experimentation. A search of the ATCC website for the accession numbers did not identify any information or there having been any deposits made under these accession nos (See attached search output for each accession no.). Further, the only disclosure for the deposits appears on p. 14, ¶3 of the specification where no description of the hybridomas is provided much less any relevant information on the repository and the date of deposit. Absent a further showing that the deposits have actually been made, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell lines; (2) a cell line which produces the chemically and functionally

distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If a deposit is made after the effective filing date of the application for patent in

the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

Enablement

16. Claims 1-3, 5, 9, 11-13, 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for recombinant antibody constructs comprising an anti-idiotypic Lewis Y- or anti-idiotypic Sialyl-Tn- or anti-idiotypic Globo H- mimicking hypervariable region fused to murine IgG2a constant region and designed for primate immunization, does not reasonably provide enablement for any antibody comprising "at least part of a murine IgG2a subtype sequence" or an IgG1 antibody containing any part of a murine IgG2a subtype within the constant domain and still retain antigen binding and immunogenicity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They

include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

The claims encompass antibodies comprising any murine IgG2a subtype region which could include VH domains, VL domains, CRDs and/or Fc domains designed for immunization of primates and comprising a hamster or primate glycosylation (Claim 1) where the antibody contains an epitope specific for a TAA (Claim 2) or a mimotope for a TAA (Claim 3) or a Lewis-Y minotope (Claim 5), where the antigen is a carbohydrate Lewis-Y, Sialyl-Tn or Globo H (Claims 10, 29 and 30), and Claims 11 and 12 encompass the murine IgG2a subtype region being inserted anywhere into the constant region of an IgG1 antibody much less within the CH1, hinge, CH2 and CH3 regions and any combination thereof, and the antibody is an anti-idiotypic antibody to Mabs produced by the hybridomas of having ATCC deposit nos. HB 9324 or HB 9347 (Claim 13).

Disclosure in the Specification

The specification makes a general disclosure for anti-idiotypic antibodies against Lewis-Y (pp. 5, 12, 13, 14 and 36), Sialyl-Tn (p. 12) or Globo H (p. 12) carbohydrate antigens. The specification discloses an anti-idiotypic antibody for the Lewis-Y antigen in Example 8 where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed

for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4. The immunogenicity is reported to be improved over the parent antibody, IGN301 wherein the anti-idiotypic antibody produces a strong IgG response against Lewis-Y expressing epithelial cancer cells. The antibody is expressed in HEK293 cells, transformed human embryonic kidney cell cultures so would result in primate glycosylation.

It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications that would allow antigen recognition and proper folding and assembly of the antibody, and the specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations.

Prior Art Status: Single CDR-domain Antibodies

The claims encompass immunogenic antibodies comprising any amino acid sequence from any murine IgG2a. The claims encompass comprising antibodies having less than than the full complement of VH/VL CDRs from a given parent antibody are inclusive of single CDR domains. Applicants have not shown that any isolated anti-idiotypic antibody against any carbohydrate antigen much less the Lewis-Y, Sialyl-Tn or Globo H carbohydrate antigens, and having anything less than a full complement of VH/VL CDRs from a parent anti-Lewis Y or anti-Sialyl-Tn or anti-Globo H antibody would retain the antigen binding for the repective epitope or antigen. In fact there are

numerous publications acknowledging that the conformation of CDRs as well as frameworks influence binding of antibodies.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

Pascalis *et al.* The Journal of Immunology (2002) 169, 3076-3084 demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* (2003) BBRC 307, 198-205, which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is

demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* (2002) J. Mol. Biol. 320, 415-428, additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* (2007) Mol. Immunol. 44: 1075-1084 describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* J. Mol. Bio. (1999) 293, 865-881 describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* J. Mol. Biol. (1999) 294, 151-162 state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do

not support that it was clearly established, that anything less than both the VH and VL domains are sufficient to define the binding specificity of an antibody, and that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR (or less than full complement of VH CDR1-3 and VL CDR1-3).

Analyzing applicants own disclosure, there are no working examples for any hybrid or recombinant anti-idiotypic carbohydrate antibody having less than a complementary VH/VL domain pairing obtained from a parent antibody. Further, there are no examples of using single VH or VL domains or a single CDR domain of a heavy chain and/or a light chain from any murine IgG2a isotype in just any framework and producing an anti-idiotypic antibody that binds a carbohydrate antigen as broadly claimed or suggested.

Prior Art Status for Single Variable Domain Antibodies

The claims encompass any immunogenic anti-idiotypic antibody comprising at least a part of a murine IgG2s subtype amino acid sequence and the claims are not limited to which portion of the IgG2a molecule is intended. Thus it is not expected that the anti-idiotypic antibody having only a single VH or VL domain would retain its binding properties and therefore be immunogenic in a primate.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding. Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/ Undue Experimentation/Skill in the Art

Furthermore, while the level of skill required to generate the anti-idiotypic antibodies is that of a molecular biologist or molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the modified antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody) in a BIAcore assay, and then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was

available at the time of application filing, but the amount of experimentation required to generate even a single FR- and/or CDR-modified antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the FR and CDR amino acid substitutions encompassed by the claims would result in *just any* anti-idiotypic antibody clone having retained the carbohydrate antigen binding activity (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 1-3 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Hellstrom et al. (EP-A-0759442; published 2/26/97; cited in the IPER report enclosed with the filing of 10/7/05 and cited in the IDS of 8/22/07).

The interpretation of the claims is discussed supra.

Hellstrom discloses an anti-idiotypic murine IgG2a antibody against a tumor-associated carbohydrate antigen L6 (p. 43, last paragraph; p. 46, line 35- p. 48, line 8; Table XVI) which has improved ADCC measured in vitro with human effector cells and human cancer cell lines. Helstrom discloses recombinant forms of the antibodies including chimeric antibodies (p. 7 lines 55-58). It is the Examiner's position that these disclosed antibodies would act in the same manner as those claimed, i.e. retain equivalent inhibition capacity and produce immune response against carbohydrate-expressing cells. Further it is the Examiner's position that chimeric antibodies could be expressed under appropriate conditions where the glycosylation of the antibody was hamster or primate.

10. Claims 1-3, 5, 9 11-13, 29 and 30 are rejected under 35 U.S.C. 102(e) as being unpatentable over Eckert et al. (US 20050163768; published July 28, 2005; with priority to March 5, 2002 or earlier for the BR55-2 antibodies, BR55-2/IgG3 and BR55-2/IgG2).

The interpretation of the claims is discussed supra.

Eckert discloses anti-idiotypic IgG1 antibodies against BR55-2 (HB9324 and HB 9347) useful for active tumor immunotherapy. The disclosed BR55-2 antibodies bind the Y-tetrasaccharide antigen, which is expressed on the surface of human

adenocarcinoma cells of breast, colon and lung. The Lewis Y (Le(y)) antigen is a difucosylated tetrasaccharide and accordingly these molecules are one in the same would bind the same binding moieties. These same anti-idiotypic BR55-2 antibodies were used to produce anti-anti-idiotypic antibodies in rhesus monkeys. It is the Examiner's position that the antibodies produced in rhesus monkeys would be primate glocosylated and would act in the same manner as those claimed, i.e. retain equivalent inhibition capacity and produce immune response against Lewis Y carbohydrate-expressing cells. Further, because Eckert describes making chimeric and humanized antibodies with the BR55-2 antibodies it would be inherent to the method that one of skill in the art could also make recombinant anti-idiotypic antibodies by engineering different IgG2a regions from an anti-idiotypic antibody into an IgG1 background for example.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/Larry R. Helms/
Supervisory Patent Examiner